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EDITORIAL

A new possibility: gene-expression-based diagnostics for presymptomatic diagnosis of hospital-acquired infections

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Early and accurate diagnosis leading to timely treatment of sepsis remain unsolved difficult problems [1]. It is often difficult to decide whether to prescribe antibiotics to a patient presenting with signs and symptoms of sepsis, since both overtreatment and undertreatment can cause harm [2, 3]. The diagnosis of hospital-acquired infections, in particular, is further complicated by (1) the lack of an obvious 'time zero' of presentation and (2) the patient's response to the ailment that originally brought them to the hospital. The post-surgical patient (or post-trauma patient) poses a particular challenge in the diagnosis of nosocomial infection, as abnormal vital signs are expected in response to surgery or trauma. For example, even with leak rates of 4% following bowel resection, most patients have persistent vital sign abnormalities or leukocytosis [4].

However, surgical patients also present an opportunity for early diagnosis of infection, since biological parameters can be serially and frequently measured in peripheral blood (or other type of) samples during the postoperative course. The hypothesis is that early deviations in informative biomarkers may allow for early treatment of postoperative infections, thereby sparing the patient the downstream complications of undertreated sepsis. This possibility is supported by data showing that serial C-reactive protein or procalcitonin measurements could be used to predict infection in community-acquired as well as in infections acquired in the intensive care unit (ICU) in both medical and surgical patients [5–8].

Recent technological developments have enabled 'omics' (genomics, transcriptomics, proteomics, or metabolomics) measurements to identify, characterize, and quantify novel biomarkers and systems-level understandings of disease. This type of spatial and temporal characterization of the host–pathogen interactions has much potential to advance the understanding of acute infections and sepsis and potentially transform its therapeutical approach [9].

In the current issue of Intensive Care Medicine [10], Lukaszewski et al. performed a huge study set out to identify transcriptomic biomarkers for early diagnosis (in particular, presymptomatic diagnosis) of infection and potential progress to associated organ dysfunction. To this end, gene expression signatures were retrospectively generated from peripheral blood postoperative samples that were serially collected from patients undergoing elective (mostly abdominal) surgery. From an initial multicentric cohort of 4385 patients, a clinical advisory panel identified 154 patients with postoperative infection, of whom 98 progressed to sepsis. These patients were age-, sex- and procedure-matched with 151 patients with an uncomplicated recovery and 148 patients with postoperative inflammation without infection. These patient groups were further divided into an initial discovery (63 infected patients) and a training/validation (91 infected patients) cohort. The groups in the initial discovery cohort were compared in the three days preceding the symptom onset using microarray transcriptomic profiling which led to the identification of 80 transcripts with power to discriminate between the groups. A random forest-based classification approach in conjugation with

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Boruta was used to explore the RT-qPCR data and to reduce these 80 transcripts down to 25. These included a 7 gene set that could discriminate between infection and SIRS− models, a 12-gene set that distinguished between infection and SIRS+ models and finally an 8 gene set that could separate sepsis from uncomplicated infection. The authors then used a machine learning approach to build predictive models in the classification cohort. With this strategy, high sensitivity was achieved across all comparisons (AUC ranging from 0.785 to 0.942). However, while specificity was also high when comparing infected and non-infected SIRS+ (0.838) and SIRS− (0.776) patients, it yielded a very weak specificity for the comparison between sepsis and uncomplicated infection (0.217).

There are some limitations to this study that decrease its generalizability and significance potential, as acknowledged by the authors. The discovery and validation cohorts are small; the study population is fairly homogeneous (mostly white, male, undergoing abdominal surgery); and perhaps most importantly, there is no independent validation cohort for the signatures. Also, to be clinically useful, any gene expression signature would have to be transitioned to scalable diagnostic platform.

Another issue is that the dissociation of inflammatory signs from postoperative infections, coupled with the relative rarity of those postoperative infections, makes implementation of a tool theoretically very difficult. For instance—how would a clinician decide which patients need the diagnostic if many look potentially inflamed? If a majority has some sign of inflammation, will we use a new tool on the majority of new patients? In particular, the authors propose this tool to treat 'presymptomatic' patients, which by definition means all patients must be screened prior to major symptom onset. It is unclear which postoperative day would be the 'right' one. More importantly, if we assume an infection pretest probability of 10% (in an enriched cohort), and we imagine a test with a 74% sensitivity and 92% specificity (as the authors attained in this cohort), in a population of 1,000, with 100 true infections, the test will be positive in 146 (roughly half false positives) and miss 26 of the infections. This might be a useful addition but has to be weighed against the cost of implementing the test in all 1,000 patients.

Overall, this is a pioneering study as it shows that it is, in principle, possible to develop tests with predictive power for the presymptomatic identification of infected patients and especially those with a high risk of progress to infection associated organ dysfunction (sepsis). This constitutes a critical goal as it would allow for directed antimicrobial therapy and earlier intervention to potentially and dramatically decrease morbidity and mortality associated with sepsis. Perhaps this particular method or signature may be validated and translated into a clinical tool. Other 'omics' methods could follow a similar approach also, though the amount of work that went into this cohort would be difficult to repeat. Like with many good articles, we are left with not just answers but more questions. Having shown that presymptomatic diagnosis may be possible, now we must grapple with whether and how such an approach might be applied.

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Declarations

Conflicts of interest
LFM—None to declare. TES—employee of and shareholder in Inflammatix, Inc. PP—received fees for lecture from Gilead and Pfizer, consulting from MSD and Sanofi and unrestricted research grant from Abionic.

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